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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/743,329	12/26/2001	Michael Ploug	PLOUG 1	9896

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EXAMINER	
GUPTA, ANISH	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 04/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/743,329	PLOUG ET AL.	
	Examiner	Art Unit	
	Anish Gupta	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-66 and 69-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *59-61,63-65 and 69-96* is/are allowed.

6)☒ Claim(s) *62 and 66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10-18-01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, with the species Asp-Cha-phe-DSer-Darg-Tyr-Leu-Trp-Ser in the reply filed on 4-1-04 is acknowledged. The traversal is on the ground(s) that there is a common core between the peptides since each peptide has to be 9-mer, and it must have an amino acid corresponding to X2. For the variable X2, cannot be His, Phe, Trp, Tyr or Pro. Applicants then recite "preferred" amino acids that are allowed be defined for X2. Applicants, in essence argue, since the Markush group defines some structure for X2-X4, a common core exist. This is not found persuasive because Applicants cannot distinctly point a specific structural limitation that is common to all of the peptides. Even in the preferred embodiments, a cyclopenyl-L-alanine is structurally distinct from a cycloheptyl-L-alanine due to the difference in the cyclo-carbons. The base claim, however is not limited to preferred embodiments. Thus, the base claim contain, within it even more variability and is far from defining a designated core that each alternative embodiment must share within the Markush. To reiterate, Applicants cannot physically draw a single structural embodiment shared by the Markush.

The requirement is still deemed proper and is therefore made FINAL.

In accordance with Markush practice, a search was conducted for the elected species and was determined to be free of the prior art. The search was then extended to the rest of species in Claim 62 and the species were determined to be free of the prior art. Finally, the search was extended to the Markush claim 59 and was also determined to be free of the prior art. An office action on the merits follows below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 62 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recites numerous peptides that have underlined amino acids, and amino acids designated by small and capital letters. Some sequences contained have an underlined Cha while other do not have an underlined Cha. It is unclear the purpose of non-underlining the amino acid "cha." The claim specifically defines the underlined cha but does not define the non-underlined cha. In any account, Applicants should avoid using underline since underlining is often associated with the addition of new subject matter in amended claims. Here, the claims have not added new subject matter from the previous drafts.

Furthermore, the use of capital letters and small letters to designate L- and D- amino acid is confusing. Often in chemistry, the D-amino acid designation is made by placing the letter "D" in front of the desired amino acid. Thus, in the sequence DChaFSrYLWS, it is unclear if the sequence contains a DCha or Asp-Cha. Note that some sequences are designated with dashes while others are not. This makes the presence of D and L amino acids more confusing. Applicants are requested to amended the claims and display the three letter amino acid designation with the D-amino acid designations as they are conventionally depicted in peptide chemistry.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 66 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention is drawn to urokinase palsminogen activator inhibitors that are nine amino acids in length and have an uncommon amino acid. The peptides are effective against cancer.

(2) The state of the prior art

The art indicates that urokinase inhibitors are effective in inhibiting extracellular proteolytic activity in mammals. With respect to antitumor activity, the art is only speculative in their activity.

Applicants specification state that "blocking of uPA **may** also have other anti-tumour effects in context of cell signaling, cell adhesion and migration." (see page 1 of the specification).

(3) The relative skill of those in the art

The relative skill of the those in the art is high.

(4) The predictability or unpredictability of the art

As with all peptides in chemistry, one cannot readily ascertain the behavior of a peptide from structure alone. This due to the fact the art has recognized the difficulty in determining the three dimensional structure of a peptide solely based on structure. Ngo et al. teach that for proteins and peptides, a " 'Direct' approach t structure prediction, that of directly simulating the folding process, is not yet possible because contemporary hardware falls eight to nine orders of magnitude short of the task." (see page 493 in Ngo et al.) Accordingly, it is not known if an efficient algorithm for predicting the structure exist for a protein or peptide from it amino acid alone (see page 492 in Ngo et al.). Similarly, the Rudinger article (see the conclusions in particular) states "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study."

Furthermore, xenografts models are unpredictive of human efficacy in the treatment of cancer. Dermer states that "immunotherapy's killing power of the transformation of 3T3 cells by a mutated protooncogene, simply does not have the same significance for cells in vivo.' (See page 320). Further, "[t]he facts indicate, however, that petri dish cancer is really poor representation of malignancy, with characteristics profoundly different from human disease." (See page 320). Similar sentiments are echoed in a Science article by Trisha Gura. This article indicates that the fundamental problem in cancer research is that model systems are not predictive of in-vivo activity

(see page 1041). The article goes on to state xenograft models in mice "don't behave like naturally occurring tumors in humans--they don't spread to other tissues." (See page 1041). Further, other systems such as clonogenic assays are not always helpful since they "can't always predict how a tumor will respond to a drug in an animal" and "[s]ometimes they don't work because the cells simply fail to divide n culture." (See page 1042). In essence, the art indicates that "rodents are better predictors of human reaction to cardiovascular or anti-inflammatory agents than cancer or diseases of the central nervous system." (See Time article by Frederic Golden on page 44). Further, the Jain article states that for solid tumors, the clinical results to date have not met the high expectation obtained as a result of in in-vitro testing (see the paragraph of page 1079-1080). "Even with the best animal model, however, we still need to better understand how the process of biodistribution of various agents 'scales-up' from mouse to human. The biochemical and physiological differences between these species make this knowledge critical." Thus, the cancer animal models and cell models, although provide valuable information for delivery of therapeutics, to not correlate to human in-vivo efficacy.

(5) The breadth of the claims

The claim is drawn to drawn to a method of treating cancer in a mammal using the peptides of a broad general formula.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples

Although the specification provides guidance on how to make the peptides of the claimed invention, the specification has not provided ample guidance the effectiveness of peptides as inhibiting the growth rate of a tumor. The working examples are limited to a few peptides that illustrate the inhibition of uPA binding to uPAR on the surface of Human Carcinoma cells using

peptide monomer AE105 and AE120. Further, the specification proposes a gene-targeted mouse as a model system for he intervention of cancer invasion and/or metastasis but fails to show any data obtained form this model. Although working examples are not necessary, it has been held that in unpredictable art, such as chemical cases more may be required. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result."

Here working examples that illustrates efficacy against tumor is necessary given the state of the art. The art indicates that animal xenograft models in mice don't behave like naturally occurring tumors in humans--they don't spread to other tissues. Further, other systems such as clonogenic assays are not always helpful since they can't always predict how a tumor will respond to a drug in an animal" and "[s]ometimes they don't work because the cells simply fail to divide n culture. In essence, the art indicates that "rodents are better predictors of human reaction to cardiovascular or anti-inflammatory agents than cancer or diseases of the central nervous system. Further, the Jain article states that for solid tumors, the clinical results to date have not met the high expectation obtained as a result of in in-vitro testing. Even with the best animal model, however, we still need to better understand how the process of biodistribution of various agents 'scales-up' from mouse to human. The biochemical and physiological differences between these species make this knowledge critical. Thus, given the unpredictability associated with animal models, more is necessary than just a proposed use of a gene-targeted mouse as an animal model.

To complicate matters, one cannot determine if all of the peptides will behave similar to the two to three tested. As stated above, one cannot predict if a given modification in a peptide will have desired results in the inhibition of tumor growth. Direct approach to structure prediction, that of directly simulating the folding process, is not yet possible because contemporary hardware falls eight to nine orders of magnitude short of the task. Accordingly, it is not know if an efficient algorithm for predicting the structure exist for a protein or peptide from it amino acid alone (see page 492 in Ngo et al.). Moreover, The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study.

Finally, as stated in the previous office action, the claims are drawn to the treatment of all cancers. The specification has not shown effectiveness towards on single type of tumor. It is well known that the all cancers to not have the same mechanism of development and growth. Thus one could not assume that an agent effective against one tumor would be effective against all types of tumors.

(8) The quantity of experimentation necessary

Since, the is uncertain to predict the helical structure of amino acid sequences based on structure alone, since contemporary hardware falls eight to nine orders of magnitude short of the task, and since different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine if the peptides would be effective in slowing the growth rate of tumors in a subject having cancer.

4. Claims 59-61, 63-65, 69-96 are allowed. The prior art as a whole neither teaches nor suggest the substation of variable X2 of formula II(a) or formula II(b) as claimed. Thus, the peptides are both novel and unobvious over the prior art.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (571)272-0965. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can normally be reached on (571) 272-0974. The fax phone number of this group is (571)-273-8300.

Anish Gupta
Patent Examiner